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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/607,455	06/26/2003	Paula J. Bates	LOU01-011-US	3317

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/607,455	BATES ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/3/08; 11/3/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-16,43,46,47,51-55 and 57-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16,43,46,47,51-55 and 57-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 13-16, 43, 46-47, 51-55 and 57-62 are pending.

2. The related case statement filed November 3, 2008 has been considered. The USSN 12/041,969 should have been listed on the PTO 1449.

3. In view of the claims amendment filed August 3, 2008, the following rejections remains.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 13-16, 43, 46, 51-55, 57 and 59-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holdenrieder et al (of record, Int J Cancer 95: 114-120, March 2001; PTO 892) in view of Martelli et al (of record, J cellular Biochemistry 78: 264-277, 2000; PTO 892).

Holdenrieder et al teach a method of detecting excessive apoptosis in serum of patient with benign and malignant disease by detecting nucleosomes that are packed into apoptotic bodies (see entire document, col. 1, in particular). The reference method comprises the step of preparing a blood sample from a subject such as a human (mammal) having various diseases such as breast cancer, lung cancer, lymphoma, autoimmune inflammatory disease such as colitis,

inflammatory disease such as pancreatitis, and removing cells from the sample by centrifugation to collect serum or plasma (see page 115, col. 1, Patients, in particular), and reacting the serum or plasma with antibody that binds to nucleosomes and detecting the binding of anti-nucleosome antibody to nucleosome in ELISA assays (see page 114-115, Material and Methods, in particular). Holdenrieder et al teach the samples containing apoptotic bodies were homogenized (disrupting the apoptotic bodies) and diluted 1: 4 with incubation buffer (see page 115, second full paragraph, in particular). Holdenrieder et al teach the advantage of using serum or plasma for quantifying excessive apoptosis is that it is non invasive and easily perform method; it could be applied in daily routine and the concentration of nucleosomes in the serum reflects a snapshot of the rate of cell death at a defined time in patient before and after therapy (see page 114, col. 2, page 119, in particular).

The invention in claim 13 differs from the teachings of the reference only in that the method of detecting excessive apoptosis by reacting the sample with an antibody that binds specifically to nucleonin in apoptotic bodies instead of nucleosome in apoptotic bodies.

The invention in claim 51 differs from the teachings of the reference only in that the method of detecting excessive apoptosis by reacting the sample with an antibody that binds specifically to PARP-1 to in apoptotic bodies instead of nucleosome in apoptotic bodies.

Martelli et al teach a method of detecting apoptosis comprising preparing a sample from which cells such as HL60 have been removed from tissue culture (see page 265, col. 1, Materials and methods, Cell Culture and Induction of Apoptosis, in particular), detecting nucleolin using monoclonal antibody that binds to protein C23/nucleolin and monoclonal antibody such as C-2-10 that binds to PARP from Oncogene Research Products (see page 265, paragraph bridging col. 1 and col. 2, page 269, col. 2, fourth paragraph, Figure 7, in particular). Martelli et al further teach the method further comprises disrupting apoptotic bodies in the sample by permeabilized the cell with 0.2% Triton X-100 for 10 min (see page 265, col. 2, Immunoflorescent staining, in particular) or lysing the cells in lysis buffer (see page 266, col. 1, Polyacrylamide Gel Electrophoresis and Immunobloting of Cell Lysates, page 275, Figure 9, in particular). Martelli et al further teach apoptosis can be detected using antibody that binds to protein C23/nucleolin and/or antibody such as C-2-10 that binds to PARP and the increase rate of apoptosis are responsible for various disease such as degenerative disease, autoimmune disease, and carcinoma (see page 264, col. 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody that binds to nucleosome in the method of detecting apoptotic bodies from a subject of Holdenrieder et al for the monoclonal antibody that binds to nucleonin or monoclonal antibody that binds to PARP-1 for detecting excessive apoptosis as taught by Martelli et al.

One having ordinary skill in the art would have been motivated to detect apoptotic bodies in serum or plasma sample of a subject because Holdenrieder et al teach the advantage of using serum or plasma for quantifying excessive apoptosis in a subject is that the method is non-invasive, easily perform and convenience; it could be applied in daily routine and the concentration of nucleosomes in apoptotic bodies of the serum reflects a snapshot of the rate of cell death at a defined time in patient before and after therapy (see page 114, co.. 2, in particular).

One having ordinary skill in the art would have been motivated to detect apoptotic bodies in serum or plasma sample using any conventional antibody that binds to nucleolin and/or antibody that binds to PARP because Martelli et al teach apoptosis can be detected using such antibody that binds to protein C23/nucleolin and/or antibody such as C-2-10 that binds to PARP; the increase rate of apoptosis are responsible for various disease such as degenerative disease, autoimmune disease, and carcinoma (see page 264, col. 1, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed August 3, 2008 have been fully considered but are not found persuasive.

Applicants' position is that above-average levels of apoptotic bodies in the bloodstream have been correlated with the presence of tumors and cancers in a subject. While this statement appears to contradict the general observation that apoptotic levels are decreased in tumor and cancer cells, the statement is not absolute. Resistance to apoptosis is usually a late event in malignant progression--that is, resistance to apoptosis increases as the cancer grows and becomes metastatic. Therefore, early stage tumors can be characterized by slow overall growth, reflecting a high proliferation rate balanced by a high level of apoptosis. Even in late stage tumors with relatively low rates of apoptosis, the absolute number of apoptotic bodies can be high due to the large tumor mass.

Nucleolin and PARP-1 have been discovered to be unexpectedly convenient and reliable markers for the detection of apoptotic bodies, especially those shed into circulation. Detecting

these antigens in circulation, such as in plasma or serum, correlates with levels of apoptosis that overwhelm the usual apoptotic body-clearing systems, such as macrophages and/or neighboring cells to the site of apoptosis.

Normal, healthy subjects have undetectable levels of apoptotic bodies in the circulation, because the usual apoptotic body-clearing mechanisms would remove them before they accumulate to detectable levels. Consequently, nucleolin and PARP-1 are undetectable in the circulation of healthy subjects. The detection of nucleolin or PARP-1 in the circulation means that high levels of these proteins are present in the circulation, which correlates with excessive apoptosis.

The invention as now claimed is directed to two methods for detecting excessive apoptosis in a blood sample from a subject. One method includes reacting an antibody that binds specifically to nucleolin, to detect apoptotic bodies in the blood sample, wherein detecting high levels of nucleolin correlates with excessive apoptosis. The second method includes reacting an antibody that binds specifically to poly(ADP-ribose) polymerase (PARP-1), to detect apoptotic bodies in the blood sample, wherein detecting high levels of PARP-1 correlates with excessive apoptosis.

The rejections of the claims under 35 U.S.C. § 103 over Holdenrieder et al. in view Martelli et al., and optionally further in view Hanakhi et al., Solani et al., Gouqeon et al., Andrade et al., and/or Aihara et al., are respectfully traversed. Neither Holdenrieder et al. nor Martelli et al. provide any guidance as to the presence or absence of either nucleolin or PARP-1 in apoptotic bodies. Neither Holdenrieder et al. nor Martelli et al. correlate the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis.

Holdenrieder et al. describes nucleosomes in serum of patients with benign and malignant diseases. In the abstract, this references postulates that "the concentration of nucleosomes in serum *might* be a useful tool for monitoring the biochemical response during antitumor therapy, especially for the early estimation of therapeutic efficacy" (emphasis added). The authors note two types of cell death: "Whereas cells in the center of solid tumors mainly die via oncosis (formerly known as necrosis), cells at the margins are preferentially eliminated by apoptosis" (column 1, page 114; citations omitted). Further noted is that nucleosomes "are complexes formed from DNA and histones", and Under physiological conditions, these nucleosomes are packed into apoptotic bodies and engulfed by macrophages and neighboring cells.

However, at high rates of apoptosis, these phagocytosing mechanisms are saturated, leading to elevated concentrations of nucleosomes in the circulating blood. (column 1, page 114; citations omitted).

The applied references do not provide any guidance as to the presence or absence of either nucleolin or PARP-1 in apoptotic bodies. The applied references do not correlate the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis.

Contrary to applicants' assertion that applied references provide any guidance as to the presence of nucleolin or PARP in apoptotic bodies, Martelli et al teach nucleolin is detected in the apoptotic cells and the apoptotic bodies of the apoptotic cells using mouse monoclonal antibody MS3 to protein C23 (nucleolin) and DAPI (nuclei) see lower panels FIG 3 B and C, in particular. The staining was apparently maintained in all stages of apoptotic nuclear changes (see page 268, col. 1, Figures 3B and 3C, in particular).

Martelli et al teach the use of PARP as a marker of apoptosis and PARP is detected in the apoptotic bodies in advance stage of apoptosis using DAPI and monoclonal antibody to PARP that detects an increasing amount of PARP that migrate at approximately 85 kDa as compared to non-apoptotic cells (N) (see page 270, immunoblotting analysis, Figure 9 PARP, right lane A, in particular).

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007)* and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

Since high concentration of apoptotic bodies in serum is correlated with a higher rate of apoptosis in the circulation of patients with benign and malignant diseases, the concentration of apoptotic bodies might reveal a snapshot of the rate of cell death at a defined time, the spontaneous rate of cell death in sera of patients before therapy as well as the induced rate of cell death during and after therapy might contain important information about tumor activity and its sensitivity to therapy and the convenience of detecting apoptotic bodies in serum sample as taught by Holdenrieder and the nucleolin or PARP have been used as markers of apoptosis and antibodies that bind to nucleolin or PARP are known in the art and predictable at the time the invention was made, there would have been reasonable expectation of success in combine the references teachings to arrive at the claimed invention. An obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007).* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

7. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holdenrieder et al (of record, Int J Cancer 95: 114-120, March 2001; PTO 892) in view of Martelli et al (of record, J cellular Biochemistry 78: 264-277, 2000; PTO 892) as applied to claims 13-16, 43, 46, 51-55, 57 and 59-62 mentioned above and further in view of Hanakahi et al (of record, Proc Natl Acad Sci 94: 3605-3610, 1997; PTO 892).

The combined teachings of Holdnrieder et al and Matelli et al have been discussed supra.

The invention in claim 47 differs from the teachings of the references only in that the method of detecting excessive apoptosis in a subject wherein the antibody to nucleolin is a polyclonal antibody instead of a monoclonal antibody.

Hanakahi et al teach a recombinant human nucleolin as well as polyclonal antibody that binds to human nucleolin (see page 3607, Fig 2, in particular). The reference polyclonal antibody is specific for the human nucleolin since it detects a single band by Western blot (see 3607, Figure 2B, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody that binds to nucleolin of Martelli et al in the method of detecting excessive apoptosis in the serum of a subject of Holdenrieder et al for the polyclonal antibody that binds specifically to nucleolin as taught by Hanakahi et al.

One having ordinary skill in the art would have been motivated to substitute monoclonal for the polyclonal antibody that binds to nucleolin because the polyclonal antibody to nucleolin of Hanakahi et al is quite specific as it detects a single band by Western blot (see 3607, Figure 2B, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed August 3, 2008 have been fully considered but are not found persuasive.

Applicants' position is that Hanakhi et al., Solani et al., Gou.qeon et al., Andrade et al., and Aihara et al have only been cited for elements of dependent claims. These references do not provide any guidance as to the presence or absence of either nucleolin or PARP-1 in apoptotic bodies. These references do not correlate the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis.

The applied references do not provide any guidance as to the presence or absence of either nucleolin or PARP-1 in apoptotic bodies. The applied references do not correlate the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis.

With respect to apoptotic bodies in the blood sample is indicative of excessive apoptosis, Holdenrieder et al. teach under physiological conditions, these nucleosomes are packed into apoptotic bodies and engulfed by macrophages and neighboring cells. However, at high rates of apoptosis (excessive apoptosis), these phagocytosing mechanisms are saturated, leading to elevated concentrations of nucleosomes packed into the apoptotic bodies in the circulating blood (column 1, page 114; citations omitted). In other words, excessive apoptosis overwhelming the phagocytes, the defect in clearance lead to elevated apoptosis bodies found in blood stream. One of the markers found in apoptotic bodies is nucleosome as taught by Holdenrieder et al. However, Martelli teach other markers such as nucleolin and PARP that are also found in apoptotic bodies.

Contrary to applicants' assertion that applied references do not provide any guidance as to the presence of nucleolin or PARP in apoptotic bodies, Martelli et al teach nucleolin is detected in the apoptotic cells and the apoptotic bodies of the apoptotic cells using mouse monoclonal antibody MS3 to protein C23 (nucleolin) and DAPI (nuclei) see lower panels FIG 3 B and C, in particular. The staining was apparently maintained in all stages of apoptotic nuclear changes (see page 268, col. 1, Figure 3B,C, in particular).

Martelli et al teach PARP is detected in the apoptotic bodies of advance stage of apoptosis using DAPI and monoclonal antibody to PARP that detects an increasing amount of PARP that migrate at approximately 85 kDa as compared to non-apoptotic cells (N) (see page 270, immunoblotting analysis, Figure 9 PARP, right lane A, in particular).

With respect to the argument that none of the references correlate with the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis, it is noted that the claims recite detecting the binding of the antibody to nucleolin or PARP in the apoptotic bodies of the sample is indicative of excessive apoptosis in the subject. None of the rejected claims correlate with the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis as argued.

8. Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holdenrieder et al (of record, Int J Cancer 95: 114-120, March 2001; PTO 892) in view of Martelli et al (of record, J cellular Biochemistry 78: 264-277, 2000; PTO 892) as applied to claims 13-16, 43, 46, 51-55, 57 and 59-62 mentioned above and further in view of Solani et al (of record, Eur J Histochem 45: 389-392, 2001; PTO 892).

The combined teachings of Holdnrieder et al and Matelli et al have been discussed supra.

The invention in claim 58 differs from the teachings of the references only in that the method of detecting excessive apoptosis in a subject wherein the antibody to PARP-1 is a polyclonal antibody instead of a monoclonal antibody.

Soldani et al teach a method of detecting apoptosis using polyclonal antibody that binds to PARP-1 (see page 390, col. 1 Materials and Methods, in particular). Soldani et al teach PAPR-1 is detected in the same cell using TUNEL assay, which is another assay for detecting apoptosis (see page 391, Fig 1 d, h, in particular). Soldani et al teach in autoimmune disease such as SLE, there is a defective clearance of apoptotic bodies and it is the accumulation of apoptotic bodies

that could trigger the production of autoantibodies against nuclear components expressed on the apoptotic bodies (see page 390, col. 2, last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody that binds to PARP-1 of Martelli et al in the method of detecting excessive apoptosis in a subject of Holdenrieder et al for the polyclonal antibody that binds to PARP-1 as taught by Soldani et al.

One having ordinary skill in the art would have been motivated to substitute the monoclonal antibody for the polyclonal antibody that binds to PARP-1 because the polyclonal antibody of Solani et al has been shown to detect apoptosis and confirm using the DNA fragmentation TUNEL assay which can be visualized using double immunoflorescence detection assays (see page 391, Fig 1 d, h, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed August 3, 2008 have been fully considered but are not found persuasive.

Applicants' position is that Hanakhi et al., Solani et al., Gou.qeon et al., Andrade et al., and Aihara et al have only been cited for elements of dependent claims. These references do not provide any guidance as to the presence or absence of either nucleolin or PARP-1 in apoptotic bodies. These references do not correlate the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis.

The applied references do not provide any guidance as to the presence or absence of either nucleolin or PARP-1 in apoptotic bodies. The applied references do not correlate the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis.

With respect to apoptotic bodies in the blood sample is indicative of excessive apoptosis, Holdenrieder et al. teach under physiological conditions, these nucleosomes are packed into apoptotic bodies and engulfed by macrophages and neighboring cells. However, at high rates of apoptosis (excessive apoptosis), these phagocytosing mechanisms are saturated, leading to elevated concentrations of nucleosomes packed into the apoptotic bodies in the circulating blood (column 1, page 114; citations omitted).

Contrary to applicants' assertion that applied references do not provide any guidance as to the presence of nucleolin or PARP in apoptotic bodies, Martelli et al teach nucleolin is detected in the apoptotic cells and the apoptotic bodies of the apoptotic cells using mouse monoclonal antibody MS3 to protein C23 (nucleolin) and DAPI (nuclei) see lower panels FIG 3 B and C, in particular. The staining was apparently maintained in all stages of apoptotic nuclear changes (see page 268, col. 1, Figure 3B,C, in particular).

Martelli et al teach PARP is detected in the apoptotic bodies of advance stage of apoptosis using DAPI and monoclonal antibody to PARP that detects an increasing amount of PARP that migrate at approximately 85 kDa as compared to non-apoptotic cells (N) (see page 270, immunoblotting analysis, Figure 9 PARP, right lane A, in particular).

With respect to the argument that none of the references correlate with the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis, it is noted that the claims recite detecting the binding of the antibody to nucleolin or PARP in the apoptotic bodies of the sample is indicative of excessive apoptosis in the subject. None of the rejected claims correlate with the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis as argued.

9. Claims 14, 16, 52 and 54 are mentioned are rejected under 35 U.S.C. 103(a) as being unpatentable over Holdenrieder et al (of record, Int J Cancer 95: 114-120, March 2001; PTO 892) in view of Martelli et al (of record, J cellular Biochemistry 78: 264-277, 2000; PTO 892) as applied to claims 13, 15, 43, 46, 51, 53, 55, 57 and 59-62 mentioned above and further in view of Gougeon et al (of record, J Immunology 156: 3509-3520, 1996; PTO 892) or Andrade et al (of record, Apoptosis in Systemic Lupus Erythematosus", Rheumatic Disease Clinics of North America vol, 2, pages 215-227, May 2000; PTO 1449) or Aihara et al (of record, Human Pathology 25(8): 797-801, 1994; PTO 1449).

The combined teachings of Holdnrieder et al and Matelli et al have been discussed supra.

The invention in claims 14 and 52 differs from the teachings of the references only in that the method of detecting excessive apoptosis in a subject wherein the subject having Acquired Immunodeficiency Syndrome or an autoimmune disease.

The invention in claims 16 and 54 differs from the teachings of the references only in that the method of detecting excessive apoptosis in a subject wherein the subject is suspected of having prostatic carcinoma.

Gougeon et al teach patients infected with HIV having Acquired Immunodeficiency Syndrome have increased apoptosis of peripheral lymphocytes (see entire document, abstract, page 3517, in particular). Significant correlation was found between the intensity of spontaneous and activation-induced apoptosis in total lymphocytes and disease progression (see page 3517, col. 2, in particular).

Andrade et al teach patients with autoimmune disease such as systemic lupus erythematosus (SLE) have defects in clearance and degradation of apoptotic corpse (apoptotic bodies) in these patients (see page 221-222, in particular). Because of the defect in the clearance of apoptotic bodies and autoantigens clustered and concentrated on the surface blebs of apoptotic cells led to the generation of autoantibodies that recognize the surface of the apoptotic cells (see page 217 and 219, last paragraph, in particular).

Aihara et al teach the frequency of apoptotic bodies correlates with higher Gleason Grade in prostate cancer, which is predictive of tumor progression (see abstract, Figure 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cancer patient in the method of detecting excessive apoptosis of Holdnrieder et al and Matelli et al for the patient with Immunodeficiency Syndrome as taught by Gougeon et al, or the patient with autoimmune disease such as systemic lupus erythematosus (SLE) as taught by Andrade et al or the patient with prostate cancer as taught by Aihara et al.

One having ordinary skill in the art would have been motivated to substitute the patient because Gougeon et al teach patients infected with HIV having Acquired Immunodeficiency Syndrome have increased apoptosis of peripheral lymphocytes (see entire document, abstract, page 3517, in particular). Andrade et al teach that patients with autoimmune systemic lupus erythematosus (SLE) have increased apoptosis and the defects in clearance and degradation of apoptotic corpse (apoptotic bodies) that led to autoimmunity in these patients (see page 221-222, in particular). Aihara et al teach the frequency of apoptotic bodies correlates with higher Gleason Grade in prostate cancer, which is predictive of tumor progression (see abstract, Figure 2, in particular). One having ordinary skill in the art would have been motivated to detect excessive apoptosis in patient because Holdenrieder et al teach the advantage of using serum or plasma for quantifying excessive apoptosis in a subject is that the method is non-invasive and easily perform; it could be applied in daily routine and the concentration of apoptotic bodies in the serum reflects a snapshot of the rate of cell death at a defined time in patient before and after therapy (see page 114, co.. 2, in particular). Martelli et al teach apoptosis can be detected using any antibody that

binds to protein C23/nucleolin and/or antibody such as C-2-10 that binds to PARP; the increase rate of apoptosis are responsible for various disease such as degenerative disease, autoimmune disease, and carcinoma (see page 264, col. 1, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed August 3, 2008 have been fully considered but are not found persuasive.

Applicants' position is that Hanakhi et al., Solani et al., Gou.qeon et al., Andrade et al., and Aihara et al have only been cited for elements of dependent claims. These references do not provide any guidance as to the presence or absence of either nucleolin or PARP-1 in apoptotic bodies. These references do not correlate the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis.

The applied references do not provide any guidance as to the presence or absence of either nucleolin or PARP-1 in apoptotic bodies. The applied references do not correlate the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis.

With respect to apoptotic bodies in the blood sample as indicative of excessive apoptosis, Holdenrieder et al. teach under physiological conditions, these nucleosomes are packed into apoptotic bodies and engulfed by macrophages and neighboring cells. However, at high rates of apoptosis (excessive apoptosis), these phagocytosing mechanisms are saturated, leading to elevated concentrations of nucleosomes packed into the apoptotic bodies in the circulating blood (column 1, page 114; citations omitted).

Contrary to applicants' assertion that applied references provide any guidance as to the presence of nucleolin or PARP in apoptotic bodies, Martelli et al teach nucleolin is detected in the apoptotic cells and the apoptotic bodies of the apoptotic cells using mouse monoclonal antibody MS3 to protein C23 (nucleolin) and DAPI (nuclei) see lower panels FIG 3 B and C, in particular. The staining was apparently maintained in all stages of apoptotic nuclear changes (see page 268, col. 1, Figure 3B,C, in particular).

Martelli et al teach PARP is detected in the apoptotic bodies of advance stage of apoptosis using DAPI and monoclonal antibody to PARP that detects an increasing amount of

PARP that migrate at approximately 85 kDa as compared to non-apoptotic cells (N) (see page 270, immunoblotting analysis, Figure 9 PARP, right lane A, in particular).

With respect to the argument that none of the references correlate with the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis, it is noted that the claims recite detecting the binding of the antibody to nucleolin or PARP in the apoptotic bodies of the sample is indicative of excessive apoptosis in the subject. None of the rejected claims correlate with the presence of either nucleolin or PARP-1 in a blood sample with excessive apoptosis as argued.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

13. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
November 21, 2008